

Office-Based Management of Urticaria

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ABSTRACT

Urticaria is a common pruritic skin disorder that is often seen in the office and varies in severity and chronicity. The etiologic cause is frequently not identifiable. Urticaria may be associated with physical factors and triggers, including foods or medications. A significant percentage of patients with chronic urticaria have circulating autoantibodies directed toward immunoglobulin-E or the high-affinity receptor for immunoglobulin-E (FcεRI), or have antithyroid antibodies that might play a role in the activation of the final common pathway in urticaria: mast cell activation and degranulation. Management begins with a careful investigation and elimination of eliciting factors when identified, followed by treatment of underlying disease. Antihistamines are the current mainstay of pharmacotherapy for urticaria, which provide symptomatic relief in most cases. In severe cases, corticosteroids, hydroxychloroquine sulfate (Plaquenil; Sanofi-Synthelabo, New York, NY), and immunosuppressive agents, including cyclosporin, are sometimes used by specialists.

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Urticaria is a common skin disorder, affecting 12% to 24% of individuals at some point in their lifetime. It is characterized by erythematous, circumscribed, and pruritic wheals involving the superficial layers of the skin. The skin lesions are the result of mediator release from cutaneous mast cells. This disorder may be mild and episodic, or severe and chronic. Urticaria can lead to serious quality of life impairment comparable to that of patients with cardiovascular disease.¹ Angioedema occurs in approximately 40% of cases of urticaria and is caused by mast cell mediator release in the subcutaneous tissue and deep dermis.

Urticaria is classified according to its chronicity into acute (<6 weeks' duration) and chronic (>6 weeks' duration) forms (Table 1). It may occur spontaneously or on exposure to physical factors or contact with allergens. Chronic urticaria is less common than acute urticaria. The majority of cases of chronic urticaria lack an identifiable physical factor or eliciting agent. There is evidence of au-

toimmune dysregulation in up to 50% of individuals with chronic idiopathic urticaria involving autoantibodies to the high-affinity immunoglobulin (Ig)E receptor (FcεRI) or less commonly to IgE.²

Patients with urticaria who do not respond to conventional therapy with antihistamines, or when there is a suspicion for an underlying systemic disease, can benefit from specialty consultation. A consultation with an allergist/immunologist is recommended when the eliciting factor is unknown, seems to be immune related as in food sensitivity, or is autoimmune in nature. Such consultations allow for specialized diagnostic testing and recommendations for medical therapies.

PATHOGENESIS

Mast cell activation and mediator release is a complex process involving both immune and nonimmune pathways. In a patient sensitized to a food, insect venom, or medication, IgE-mediated activation of dermal mast cells may result in acute urticaria (Figure 1). Mast cells also might degranulate and cause hives through non-immune mechanisms such as observed in physical urticarias (cholinergic, cold-induced, delayed pressure, vibratory, solar, and aquagenic urticarias; and dermatographism).

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Autoantibodies to the α subunit of the Fc receptor of the IgE molecule (Fc ϵ RI) can activate basophils to release histamine in vitro. This response may be augmented by complement activation and the production of C5a (Figure 2). Also supporting an autoimmune pathogenesis of chronic urticaria is the increased prevalence of antithyroid antibodies and thyroid dysfunction in some patients. Twenty-seven percent of patients with chronic urticaria have either or both antithyroglobulin antibody and antimicrosomal antibody, and 19% have abnormal thyroid function.³ Other non-IgE-mediated mast cell degranulators include radiocontrast media and medications, including morphine, codeine, and vancomycin.

DIAGNOSIS

Key questions from the history include the following: Was the reaction actually anaphylaxis or was it simple urticaria/angioedema? What is the frequency, duration, shape, distribution, and time of onset of the hives (Table 2)? Is there a relationship to any ingested food, medication, contactant,

insect bite/sting, or physical stimuli in onset and chronicity? Is there any associated pruritus, pain, swelling, fatigue, or other indicators of infections or inflammatory conditions? Is there any use of nonsteroidal anti-inflammatory drugs, angiotensin-converting inhibitors, or other medications or herbal remedies? Is there a history of surgical implants? What has been the response to therapy in the past?

The differential diagnosis is broad. It includes erythema multiforme minor that presents with a prodrome of constitutional symptoms followed by pleomorphic cutaneous lesions; papular responses secondary to insect bites that tend to occur on the lower extremities and persist for more than 24 hours; urticaria pigmentosa secondary to systemic mastocytosis; collagen vascular disorders, including urticarial vasculitis; allergic contact dermatitis; and familial disorders, including hereditary angioedema and familial cold autoinflammatory syndrome.

DIAGNOSTIC EVALUATION

Physical examination should determine the characteristics of the hives, the presence of other associated skin lesions, and any indications of systemic disease. Patients should be screened for dermatographism by attempting to elicit a wheal after application of linear skin pressure (Figure 3). Antihistamines should be withheld for 36 to 72 hours before determination of dermatographism or skin testing with allergic extracts to prevent false-negative results.

It is unusual for a food allergy to be the basis of chronic urticaria, and most patients with food-associated acute urticaria are aware of the association. In acute urticaria when there is a suspicion of a food allergy, patients should be evaluated by an allergist for food sensitivities using skin prick or ImmunoCAP (Phadia AB, Uppsala, Sweden) and radioallergosorbent testing for evidence of food allergen-specific IgE. If the clinical history and testing indicate that the urticaria is likely food induced, the suspected food(s) should be avoided. Reintroduction may require a blinded or open food challenge conducted under direct medical supervision by personnel who are trained to diagnose and treat anaphylaxis.

Although chronic urticaria may occur coincident with the presence of a primary disease process, for instance, a viral infection, resolution of the underlying condition may not lead to resolution of urticaria. Some patients with chronic urticaria and antithyroid antibodies improve with thyroxine treatment, but there is no correlation between the clinical response and the level of thyroid antibodies. Infection with

CLINICAL SIGNIFICANCE

- Urticaria is a common pruritic skin disorder that varies in severity and chronicity.
- A subset of patients with chronic urticaria have circulating autoantibodies directed toward IgE or the high-affinity receptor for IgE (Fc ϵ RI), or have antithyroid antibodies.
- Antihistamines are the current mainstay of pharmacotherapy for urticaria, which provide symptomatic relief in most cases.
- A consultation with an allergist/immunologist is recommended when the eliciting factor is unknown.

Table 1 General Classification of Urticaria

Type	Characteristic
Acute	Duration < 6 wk
Chronic	Duration > 6 wk
Physical Urticarias	
Dermatographism	"Draw on skin," from mechanical pressure
Cold	Induced by exposure to cold water/air
Delayed pressure	Hives 4-6 h after applied pressure
Solar	Induced by exposure to 2800-5000 Å wavelength of sunlight
Heat, localized	Induced by exposure to heated material
Heat, generalized, or cholinergic	Punctate wheals associated with exposure to heat, exercise, and anxiety
Exercise-induced (anaphylaxis)	Large hives induced by exercise alone
Aquagenic	Induced by contact with water
Vibratory	Induced by vibratory forces
Collagen vascular disease	
Urticarial vasculitis	Associated with individual lesions lasting > 24 h

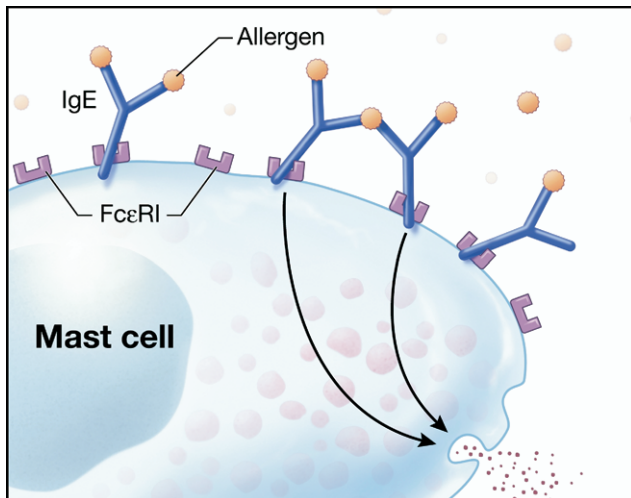


Figure 1 Acute urticaria. Allergen crosslinks IgE bound to FcεRI on mast cells causing activation and degranulation. FcεRI, High-affinity IgE receptor; Ig, immunoglobulin.

Helicobacter pylori has been suggested in a few reports to be a cause of chronic urticaria, but in most studies a definitive relationship has not been identified.⁴ Examples of other reported conditions associated with urticaria include endocrine tumors, cryoglobulinemia, and autoimmune disorders such as systemic lupus erythematosus (Table 3).

Most cases of acute urticaria resolve spontaneously, and diagnostic testing is not required or is modest. The laboratory evaluation for chronic urticaria is limited (Table 2). A complete blood count, blood chemistries, and urinalysis are usually normal. If an underlying rheumatologic disorder is suspected, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, and rheumatoid factor should be performed. When urticarial lesions persist more than 24 hours and there is associated petechia or purpura, a skin biopsy is warranted. Histologic evidence of leukocytoclasia (neutrophilic infiltration with fragmentation of nuclei) is a characteristic feature of urticarial vasculitis. Although most autoimmune diseases are not associated with urticaria, Hashimoto's disease is a well-known exception. Given this association, thyroid studies including antithyroglobulin and antimicrosomal antibodies are often informative.

The elicitation of a hive after the injection of a patient's own serum during active urticaria, known as the autologous serum skin test, has been used for an in vivo method to suggest the presence of autoantibodies in chronic urticaria. However, the relatively low sensitivity and specificity of this test necessitate the use of other confirmatory assays for the diagnosis of chronic autoimmune urticaria. The presence of functional IgG anti-FcεRI or anti-IgE autoantibodies can more definitively be detected using basophil mediator release assays.⁵ Basophil mediator release has been correlated with expression of the basophil activation markers CD63 and CD203 determined by flow cytometry.⁶ Other assays to determine the presence of IgG anti-FcεRI or

anti-IgE autoantibodies are less specific for urticaria, because they may be present in patients without urticaria and in other autoimmune diseases such as pemphigus vulgaris and dermatomyositis.

GENERAL MANAGEMENT

Avoidance of identified triggers of urticaria is the first step in management. For example, in pressure urticaria, weight-dependent areas of the body are more affected and the contact of the strap of a heavy bag over the shoulder may elicit symptoms. Proper protection from cold air, wind, and water should be emphasized in patients with cold-induced urticaria. Treatment for *H. pylori*, bacterial sinusitis, and parasitic and other infectious or inflammatory disease should be instituted as appropriate.

DIETARY MANAGEMENT

When IgE-mediated food allergy manifests with urticaria, the specific food should be avoided. Some patients with chronic urticaria have responded to strict diets low in food additives, food colorings, and highly allergenic foods (eg, tree nuts, peanuts) even when there is no evidence of increased specific IgE to any food items.⁷ Larger controlled studies are needed to further define the specific components in the diet that may contribute to chronic urticaria.

PHARMACOTHERAPY

The mainstay of pharmacotherapy for both acute and chronic urticaria is anti-H₁ antihistamine (Table 4). In patients with mild chronic urticaria, low-sedating antihistamines, such as loratadine, cetirizine, and fexofenadine, decrease the intensity of hives and pruritus and are considered first-line

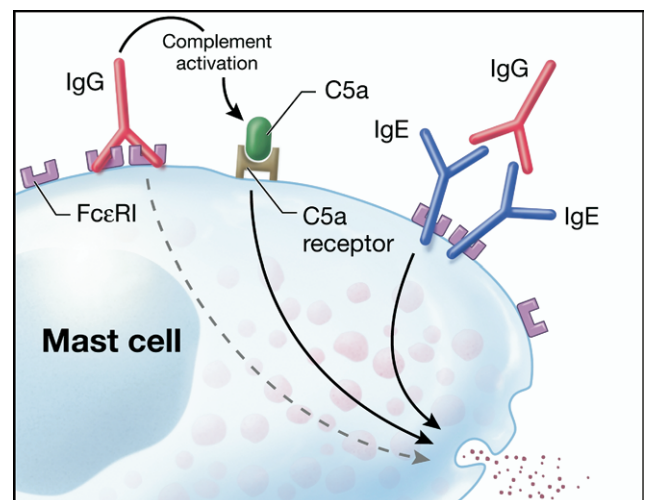


Figure 2 Mechanisms of autoimmune urticaria. Activation of mast cells and basophils in vitro through IgG autoantibodies directed toward the α subunit of FcεRI or IgE itself. This response is augmented by complement activation and production of anaphylotoxin, C5a. Ig, Immunoglobulin.

Table 2 Diagnostic Evaluation

Type of Urticaria	Diagnostic Testing	Additional Testing
Acute urticaria	Skin prick testing or ImmunoCAP (Phadia AB, Uppsala, Sweden)/RAST for foods, elimination of eliciting factor when indicated	Food challenge when indicated
Chronic urticaria	Complete blood count, ESR or CRP, total IgE, autoimmune tests, anti-thyroid antibodies, ANA, chronic infections, ie, <i>Helicobacter pylori</i>	Autologous serum skin test, basophil mediator assay, flow cytometry using basophil activation markers: CD63 or CD203c
Physical urticaria		
Dermatographism	Linear stroking of skin causes a wheal	
Cold	5- to 10-min application of ice cube causes a wheal on removal within 5 min	Cryoglobulins
Delayed pressure	Application of pressure perpendicular to skin over specified time causes swelling within 6 h	
Solar	Irradiation with UV solar stimulator or visible light	Evaluate for other photosensitivities
Local heat	Apply warm material to arm	
Cholinergic	Exercise challenge	Intradermal injection of methacholine produces a localized hive
Aquagenic	Exposure to water for 20 min	
Vibratory	Vortex for several minutes	
Collagen vascular disease		
Urticarial vasculitis	Skin biopsy, complete blood count, ESR, ANA	

RAST = radioallergosorbent test; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; Ig = immunoglobulin; ANA = antinuclear antibody; UV = ultraviolet.

therapy. Sedation and impairment of performance is a concern when using sedating antihistamines, yet these side effects may wear off in 1 to 2 weeks.⁸ Doxepin, a tricyclic antidepressant, is an effective antihistamine but may be associated with sedation and anticholinergic side effects.

There is a rationale for the addition of an H₂ receptor antagonist based on the presence of H₂ receptors in the skin. Small studies attest to their therapeutic efficacy when used

in conjunction with H₁ blockers.⁹ However, this may be due to their pharmacokinetic influence rather than a direct histaminic receptor antagonistic effect.

When antihistamines are not adequate, corticosteroids are usually effective. For acute urticaria in this setting, a short course of high-dose corticosteroids is often used, but rebound urticaria is common. For chronic hives, low-dose daily or alternate-day corticosteroids are helpful when an-



Figure 3 Dermatographism. Linear stroking of skin elicits a wheal within several minutes.

Table 3 Medical Conditions Associated with Urticaria

Infectious Diseases
Bacterial (<i>H. pylori</i>)
Viral
Parasitic
Connective tissue disease
Cutaneous vasculitis
SLE
Endocrine Disorders
Thyroid disease
Malignancy
Endocrine tumors
Lymphomas
Autoimmune Disorders
Cryoglobulinemia

SLE = systemic lupus erythematosus.

Table 4 Pharmacotherapeutic Management of Urticaria

	Drug (Example)	Comments
H ₁ Antagonists	Nonsedating	Antihistamines are first-line treatment for acute and chronic urticaria.
	Desloratadine	
	Fexofenadine	
	Cetirizine	Side effects include sedation, cognitive impairment, dry mouth, and urinary retention especially at higher doses
	Sedating	
	Diphenhydramine	
	Hydroxyzine	
H ₂ Antagonists	Doxepin	Doxepin is a tricyclic antidepressant and an H ₁ and H ₂ antagonist.
	Cyproheptadine	
	Cimetidine	Recommended in conjunction with an H ₁ antagonist
Corticosteroids	Prednisone	Generally effective in severe episodes of acute and chronic urticaria
	Methylprednisolone	Often required to control urticarial vasculitis
		Titrate to most effective lowest dose or alternate day dose for long term
Leukotriene Receptor Antagonist	Montelukast	Efficacy in treatment of urticaria has not been established
	Zafirlukast	
Other Immunomodulatory/ Anti-inflammatory Agents	Thyroxine	May be effective in patients with chronic urticaria and thyroid autoimmunity
	Cyclosporine	Effective in treatment of chronic urticaria
		Monitor blood pressure and renal function
	Methotrexate	Efficacy not established
	Cyclophosphamide	Significant potential side effects
	Dapsone	
	Colchicine	
	Rofecoxib	Safety and efficacy not established
	Intravenous immunoglobulin	May be effective in chronic autoimmune urticaria
	Plasmapheresis	
	Hydroxychloroquine	May be effective in hypocomplementemic urticarial vasculitis
Other	Sulfasalazine	May be effective in delayed-pressure urticaria
	Epinephrine	Patients with acute urticaria should be trained in the use of an epinephrine auto-injector device

tihistamines fail and should be titrated to the lowest efficacious dose. Patients receiving long-term corticosteroids should be routinely monitored for bone density changes, decreases in growth (in children), and ocular side effects. Although mechanistic data suggest that leukotriene mediators play a role in allergic inflammation of the skin, there is little evidence for the effectiveness of antileukotriene drugs in the treatment of chronic idiopathic urticaria.

Patients with chronic urticaria and elevated antithyroid antibodies may improve with thyroxine treatment, but the mechanism is likely not due to a direct effect on mast cell degranulation. Selective cyclooxygenase-2 inhibitors (rofecoxib) have been shown to be beneficial in a few small studies in the treatment of chronic urticaria, given their potential to block the synthesis of prostaglandin D₂. Their safety and efficacy have not been established, and only 1 agent is presently available in the United States. When steroids are not tolerated or are inadequate in alleviating symptoms, other immunosuppressive agents may be considered. Oral cyclosporine has been shown to be effective

for chronic urticaria in randomized double-blind studies.¹⁰ This highlights the importance of inflammatory and autoimmune mechanisms in this disease. Patients with autoimmune antibodies tend to be especially recalcitrant to therapy and also might benefit from plasmapheresis and intravenous Ig.⁴ Other therapies used but not thoroughly studied include sulfasalazine (delayed pressure urticaria), hydroxychloroquine (hypocomplementemic urticarial vasculitis), methotrexate, tacrolimus, danazol, colchicine, dapsone, and cyclophosphamide (urticarial vasculitis).⁴

FUTURE DIRECTIONS

Anti-IgE monoclonal therapy theoretically should decrease the interaction of circulating autoantibody to the high-affinity IgE receptor and diminish mast cell mediator release in chronic urticaria. Such treatment has been reported to be effective in cold-induced urticaria.¹¹ Other immunomodulatory agents that might have a role in the treatment of chronic urticaria include rituximab (anti-CD 20), mycophen-

nolate mofetil, infliximab, and etanercept (tumor necrosis factor- α antagonists).

PROGNOSIS

The majority of patients with chronic idiopathic urticaria will have resolution of symptoms within 3 years from the onset of symptoms, and at 5 years 86% will be symptom free. Prognostic factors associated with a more prolonged course include the presence of angioedema and autoimmune features (anti-IgG, antithyroid antibodies).¹²

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